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Case Report

Ketamine Treatment for Intractable Pain in a Patient with Severe Refractory Complex Regional Pain Syndrome: A Case Report

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In this case report, we describe the effect of ketamine infusion in a case of severe refractory complex regional pain syndrome I (CRPS I). The patient was initially diagnosed with CRPS I in her right upper extremity. Over the next 6 years, CRPS was consecutively diagnosed in her thoracic region, left upper extremity, and both lower extremities. The severity of her pain, combined with the extensive areas afflicted by CRPS, caused traumatic emotional problems for this patient. Conventional treatments, including anticonvulsants, bisphosphonates, oral steroids and opioids, topical creams, dorsal column spinal cord stimulation, spinal morphine infusion, sympathetic ganglion block, and sympathectomy, failed to provide long-term relief from pain. An N-methyl-d-aspartate (NMDA) antagonist inhibitor, ketamine, was recently suggested to be effective at resolving intractable pain. The patient was then given several infusions of intravenous ketamine. After the third infusion, the edema, discoloration, and temperature of the affected areas normalized. The patient became completely pain-free. At one-year of follow-up, the patient reported that she has not experienced any pain since the last ketamine infusion.

Treatment with intravenous ketamine appeared to be effective in completely resolving intractable pain caused by severe refractory CRPS I. Future research on this treatment is needed.

Key words: Ketamine, Complex Regional Pain Syndrome (CRPS), treatment

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Complex regional pain syndrome I (CRPS I) causes chronic pain and predominately affects women between the ages of 36 to 46 (1). The diagnostic criteria defined by the International Association for the Study of Pain (IASP) include

1) severe pain not explained by injury, allodynia, or hyperalgesia;
2) evidence of edema, vasomotor in the location of the pain, such as cold or warm, red or cyanotic skin; and
3) no other known cause (2).

CRPS typically occurs after injury (1). Although the pathophysiology of CRPS is not completely understood, mechanisms such as neurogenic inflammation, immunological mechanisms and the role of the central nervous system have been proposed (3-6).

Management of CRPS can be challenging as this disorder is difficult to treat. Common treatments for CRPS include steroids, sympathetic block, oxygen radical scavengers, antidepressants, antiepileptics, opioids,

physical therapy, and transcutaneous electrical nerve stimulation (7). Prevention therapies such as early activity and vitamin C have been commonly prescribed. Presently, limited evidence exists for supporting the efficacy of these therapies (8-10).

Activation of N-methyl-d-aspartate (NMDA) receptors may be involved in the induction and maintenance of sensitivity to pain in several chronic pain disorders, such as neuropathic pain and CRPS. Accordingly, NMDA receptor antagonists such as ketamine and memantine can be used for the treatment of pain patients with these disorders (11-13). Although data on this indication in the literature is limited, several case reports and case series suggest efficacy for ketamine in treatment of many chronic pain disorders, including peripheral neuropathy, chronic post-traumatic neuropathic pain, postherpetic neuralgia, spinal cord injury pain, neuropathic pain associated with multiple sclerosis and Guillain–Barré syndrome, orofacial pain, CRPS, phantom limb pain, and fibromyalgia (14). We describe in this case report, a patient with severe refractory CRPS I, which, while unresponsive to conventional treatment for a period of 6 years, was completely resolved following 3 trials of ketamine infusion.

Case Report

A 41-year-old right-handed woman without past medical history injured her right elbow and wrist during an accident in 2000. She was taken to the emergency room, where an X-ray of the affected extremity was performed. The patient was discharged with the diagnosis of contusion. However, pain in this area increased gradually and she was referred to an orthopedic clinic. A second X-ray and a bone scan were stated to be normal, and the patient was diagnosed with a hidden fracture. Pain continued to increase over 4 weeks. Following the removal of the cast, the patient was referred to our interventional pain clinic at The Methodist Hospital with pain and swelling of the upper right limb.

On presentation, the patient had hyperesthesia in the right upper extremity, particularly below the elbow, to the point that she was apprehensive of the exposure of air blowing upon the affected limb. In addition, she had diffuse, non-pitting edema in the right hand and forearm. Hypertrichosis was found in her right upper extremity, and the right hand was colder compared to the left. Passive and active range of motion of her right elbow and wrist were restricted, while other limbs were completely normal.

Thrombosis was ruled out with the Color-Doppler ultrasound test. Laboratory tests (CBC, ESR, ANA, and BUN) and nerve conduction studies were within normal limits. Roentgenography of the affected arm revealed patchy osteoporosis in the carpal bones. With the patient's clinical symptoms and radiological findings, she met IASP criteria for CRPS as well as the more recently proposed clinical criteria for the diagnosis of CRPS (1,15).

The patient underwent 4 right stellate blocks with 7 mL of 0.25% bupivacaine; however, pain relief was brief and lasted only a few weeks. A thoracic surgeon performed a right stellate cervical sympathectomy via transthoracic approach, which proved to be an unsuccessful treatment. Pain spread to involve the thoracic vertebrae and right shoulder, with the onset of hyperpathia, allodynia, edema, and bluish coloration, also felt to be "spread" of CRPS I.

Due to the severity of pain and failure of treatments with amitriptyline, gabapentin, opioids, and lidocaine cream over the period of a few months, a cervical spinal stimulator was implanted. Three months after using the stimulator, with no relief from pain, a double morphine pump was implanted at T3-T4 and L4-L5. Pain was controlled for 4 months, until the patient was admitted to the hospital with symptoms of chemical meningitis, whereupon the morphine pumps were removed.

Four months later, the patient's right leg exhibited swelling and pain, and had a decrease in range of motion in the knee and ankle. All of the laboratory tests were normal, and her symptoms and signs exactly followed the pattern of her right arm. After an additional 5 months, the patient began showing the same symptoms and signs in her left arm and leg. Clinical and radiological findings pointed to a diagnosis of CRPS I in the new locations.

The patient was admitted to the hospital and started on oral steroids and intravenous (IV) lidocaine, which were ineffective for pain management. Her disorder had caused traumatic emotional problems for the patient, including depression and anxiety, and then divorce. Numerous medications were unsuccessful, including the anti-epileptic drug gabapentin, oral glucocorticoids, topical lidocaine cream, opioids, IV lidocaine, bisphosphonates, and calcitonin.

In November of 2006, after 6 years of ineffective treatment, the patient was taken to an operating room and given 50 mg IV ketamine over a period of 30 minutes under anesthetic supervision, but without se-

dation. As an optimal dosage procedure has not been identified for CPRS, a procedure similar to that of Zarate and colleagues (16) and Correll and colleagues (17) was used. Zarate et al (16) demonstrated that 0.5mg/kg over 40 minutes was an effective dose for alleviating depression. It appeared that this dose probably resulted in an NMDA effect that was sustained for at least one week, and therefore could also be effective for treating chronic pain in CPRS. One author (EE) began using this dosage and found alleviation of pain in approximately 140 cases of intractable pain of neuropathic origin or CPRS; however, he found that doses over 50 mg were more likely to result in psychiatric side effects. A fixed dose of 50 mg began to be used for adults as it appeared to be effective with less significant side effects. Hence, a 50 mg/30 min treatment was used for the patient described in this case report, and has become a standard dose for the authors for the treatment of pain.

The patient had a hypertensive reaction to the first infusion, and labetalol and hydralazine were used to abate this reaction. The patient's pain level decreased from 10 to 3 on a 10-point scale and remained at that level for 5 days. In order to prevent a second hypertensive reaction, midazolam was added to the procedure, providing a significant reduction in blood pressure and heart rate elevation in following sessions. Ketamine infusion was performed a second time on day 7, resulting in complete resolution of pain for 7 days. Ketamine was infused a third and final time, whereupon the edema, discoloration, and temperature of the affected areas normalized. Following the last infusion, the patient was completely free of pain for the first time in 6 years. After each infusion, the patient seemed slightly euphoric. She developed a migraine-like headache for 3 days after first infusion that she felt was similar to past migraines, but she did not present with any other side effects during her treatment. At a one-year follow-up visit, the patient reported continuing physical therapy and psychotherapy, and has not experienced any pain since the last ketamine infusion.

Discussion

We describe a patient with a 6-year history of severe, refractory CRPS I. The patient met IASP criteria and the new diagnostic criteria for CRPS with the presentation of hyperesthesia, allodynia, non-pitting edema, colder temperature, and hypertrichosis in affected areas (1,15). This disorder began in the right upper extremity and moved successively to her thoracic area, right lower extremity, and finally her left-sided extremities. Following treatment with IV ketamine, her pain completely resolved.

The treatment for CRPS is still debated. The treatment for this patient included anticonvulsants, bisphosphonates, oral steroids and opioids, topical creams, dorsal column spinal cord stimulation, spinal cord morphine pump, sympathetic ganglion block and sympathectomy. None of these treatments, however, provided long-term pain relief.

The pathophysiology underlying CRPS I is unclear; however, recent research suggests that sensitization of the central nervous system may be the source of pain in CRPS 1 (2). In CRPS, afferent neurons in the spinal cord may have an increased rate of release of glutamate, which may pathologically activate NMDA receptors, leading to central sensitization and hyperexcitability (12). This is supported by the finding that ketamine, an NMDA receptor antagonist, may provide pain relief in CRPS (13). After 3 infusions of intravenous ketamine (each one week apart), the patient's pain completely resolved after the last infusion and at her one-year follow-up visit, she remained pain-free.

Adverse effects of ketamine may include psychotomimetic effects, including hallucinations and agitation. Ketamine can also cause a hypertensive reaction, nausea, vomiting, increased salivation, and muscle spasms. In efforts to decrease these side effects, patients can be given ketamine in a supervised environment with co-administration of a benzodiazepine such as of the relaxant midazolam (18,19).

Conclusion

Early treatment in CRPS is well known to be beneficial for patient outcome, and can protect against complications (20). Additionally, it is our experience with refractory CRPS that performing multiple procedures can lead to a myriad of complications and prolong the course of disease. Although this is only one case report, and thus we cannot conclude anything from it, it is of interest that ketamine appeared to be beneficial after 6 years of ineffective long-term treatments. Furthermore, it is conceivable that early treatment with ketamine in CRPS, may be beneficial. Nonetheless, more research on this treatment is needed to better define its efficacy in CRPS.

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